Diagnostic Accuracy of Diffusion Weighted Magnetic Resonance Imaging in the Detection of Myometrial Invasion in Endometrial Carcinoma

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ABSTRACT

Objective: To determine the diagnostic accuracy of Diffusion-Weighted Magnetic Resonance Imaging (DWMRI) in the detection of myometrial invasion in endometrial cancer taking histopathology as gold standard.
Study Design: Cross-sectional validation study.
Place and Duration of Study: Department of Radiology, The Aga Khan University Hospital, Karachi, from January to December 2012.
Methodology: DWMRI (b-value = 50,400 and 800 s/mm^2) was performed in 85 patients of biopsy-proven endometrial carcinoma before hysterectomy using body and spine coil at 1.5 Tesla. DWI was evaluated for presence of myometrial invasion by tumor with histopathology as gold standard. Sensitivity, specificity, the negative predictive value and positive predictive value and accuracy of DWI were assessed against the gold standard.
Results: On DWI, superficial myometrial invasion was found in 42 patients and deep myometrial invasion in 43. On histopathology, superficial myometrial invasion was found in 53 patients and deep myometrial invasion in 32. Hence sensitivity, specificity, positive predictive value, negative predictive value and accuracy for the assessment of myometrial invasion by endometrial tumor on DW images was 90%, 73%, 67%, 92% and 80%, respectively. Diagnostic accuracy of diffusion-weighted magnetic resonance imaging in detection of myometrial invasion in endometrial cancer was 80%.
Conclusion: DWI is highly accurate in assessing myometrial invasion and can be used as an adjunct to routine MRI for pre-operative evaluation of myometrial invasion of endometrial cancer.

Key Words: Endometrial carcinoma. Myometrial invasion. Diffusion weighted MRI.

INTRODUCTION

Endometrial cancer is the most common gynecological malignancy of developed countries.[1] In Pakistan, no separate data regarding the prevalence of endometrial carcinoma is available; however, according to Bhurgri *et al*. cancers of female genital tract, i.e. cervix, ovary and uterus (body), encompass 13.1% of the total cancers in the females.[2] The incidence rate has shown a progressive increase for all types over the last 10 years. Internationally, endometrial cancer accounts for 6% of all cancers in women.[3]

The prognosis of endometrial cancer is dependent on a number of factors, i.e. sub-type and grade on histology, stage of tumor at diagnosis (including depth of myometrial invasion and lymph node metastasis). For most of the patients with endometrial cancer present with vaginal bleeding, the diagnosis is made by endometrial biopsy. But pre-operative staging is very important in planning proper surgical procedure and to prevent the risk of under-staging the disease and impairing the therapeutic plan. Deep myometrial invasion to the outer half of the myometrium is a poor prognostic factor, which is associated with an increased risk of pelvic and para-aortic lymph node metastases.[4] The incidence of lymph node metastases increases from 3% with superficial myometrial invasion to 46% with deep myometrial invasion.[5] The information on myometrial tumor invasion can only be obtained pre-operatively by imaging techniques and the most helpful is Magnetic Resonance Imaging (MRI).[4]

MRI is an excellent imaging method to evaluate the local stage of endometrial cancer. Endometrial cancer is depicted as thickened endometrium on T2-weighted images. The signal intensity of it may range from high signal (white) to low signal intensity (black), sometimes impossible to differentiate between normal endometrium and adjacent myometrium, on conventional MRI.[6]

DWI is a recent new imaging technique which depicts tissue characteristics based on diffusion motion of water molecules. Initially, the usefulness of this technique was established in central nervous system, and now DWI is the most accurate modality for diagnosing acute brain

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infarction.[7,8] The technique is applied to the abdominal organs and is known to depict malignant tumors with high sensitivity.[9,10]

No study pertaining to this topic is available in local literature, whereas the available international values with regard to the assessment of deep tumor invasion, sensitivity, specificity, positive and negative predictive values of DWI are 84.6%, 70.6%, 52.4% and 92.3%, respectively.[4]

The purpose of this study was to determine the diagnostic accuracy of DWI in the pre-operative assessment of myometrial tumor invasion using post-operative histopathological findings as the gold standard.

METHODOLOGY

A cross-sectional validational study, conducted at Department of Radiology, The Aga Khan University Hospital (AKUH), Karachi, from January to December 2012. The sample size was calculated on WHO software version of sample size determination in health studies. The sensitivity and specificity of DWI for assessment of greater than 50% of myometrial invasion is reported to be 88% and 85%, respectively; and reported prevalence of 3 - 46%.[5] Thus at a confidence interval of 95%, with margin of error within 10% and mean prevalence of 25%, the sample size calculated to determine greater than 50% myometrial invasion on DWI was 85 patients. Purposive non-probability sampling was used. Inclusion criteria were all patients (all ages) with proven endometrial carcinoma on biopsy of prior curettage, followed by surgery and histopathology for endometrial carcinoma at AKUH. Exclusion criteria were all patients treated with radiotherapy/chemotherapy and patients who refused to give consent. A group of 85 patients were included in this study after acquiring informed consent. All patients underwent Magnetic Resonance Imaging (MRI) of pelvis for staging before hysterectomy, with 1.5 Tesla, MRI unit. The final histopathological diagnoses, i.e. myometrial invasion and overall staging of these patients, were acquired from medical record system.

Imaging protocol included all routine sequences with addition of DWI comprising axial T1W, axial T2W, sagittal T2W and sagittal T1W post-contrast sequences. DWI comprised of axial echo-planar DWI pulse sequence, which is denoted as b-values. B-value denotes the signal strength of diffusion, i.e. b-value 0 means the diffusion signal is equal to the T2 weighted signal and b-value 800 has a very strong diffusion weighting as compared to T2 signal. Thus diffusion weighted imaging was run at the protocol set in the department for pelvic imaging (b-values = 50 s/mm^2, 400 s/mm^2 and 800 s/mm^2), using the following parameters: TR/TE, 3900/76; field of view, 38 cm; slice thickness, 4 mm; gap, 0; number of excitations, 4; matrix, 192 x 192;

3 acquisitions with 8 slices per acquisition; phase encoding direction, anterior to posterior. The time required to acquire the DWI image was set 2 minutes 30 seconds.

Image interpretation was done by a single radiologist with more than 5 years of experience in women imaging. True positive was considered if bright signal of endometrium was seen extending into more than half of dark myometrium on DWI and more than half invasion of myometrium was seen on histopathology. True negative were considered if bright signal of endometrium was not extending or extending into less than half of dark myometrium on DWI and no or less than half invasion of myometrium was seen on histopathology. MRI results was compared with findings obtained at histopathology examination.

Statistical data analysis was done using computer program SPSS (version 16). Sensitivity, specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV) and accuracy were calculated for selected criteria. Positive cases including true positive and false negative; and negative cases including true negative and false positive cases were calculated. Mean value and standard deviation was calculated for age and duration of symptoms. Stratification was also done with regards to age and duration of symptoms to see the effect of these on outcomes by using chi-square test with p-value < 0.05.

RESULTS

A total of 85 patients aged 32 - 87 years were studied (mean =59.2 ±10.24 years). More than 50% invasion was identified in 32 patients and no or < 50% in 53 patients on histopathology. MRI accurately evaluated depth of myometrial invasion in 68 out of 85 patients. Out of 68, 29 had > 50% myometrial invasion and 39 patients had no or < 50% myometrial invasion. Therefore, the sensitivity of MRI in detecting myometrial invasion of > 50% is 90%. Three patients were falsely labeled as having < 50% invasion on MRI with a negative predictive value of 92% and 14 patients were falsely labelled as having > 50% invasion on MRI with a positive predictive value of 67%. The overall accuracy in evaluating myometrial invasion in endometrial carcinoma was 80%.

The association of myometrial invasion with regard to age and duration of symptoms was assessed with chi-square test. The results are shown in Table I. Seventy-six patients were more than 50 years of age, out of which 29 patients had > 50% invasion on histopathology and 26 were correctly identified on MRI. MRI-based evaluation was highly significant in assessing myometrial invasion in patients of > 50 years with p-value of < 0.001.

Table I: Accuracy of MRI for myometrial invasion of >50% with regards to age and duration of symptoms. HP histopathology.

	N (%)	HP > 50%	MRI > 50%	p-value
Age				
≥ 50 years	76 (89.4%)	29	26	< 0.001
Duration of symptoms				
< 6 months	69 (81.2%)	26	24	< 0.001

Sixty-nine patients had < 6 months of symptom duration out of whom 26 patients revealed > 50% on histopathology. MRI correctly identified 24 patients (p < 0.001).

DISCUSSION

Surgery is the treatment of choice in patients with non-invasive or locally advanced endometrial carcinoma. Determining the presence and depth of myometrial invasion is a highly critical factor, as is used in most institutions to predict nodal metastases, since patients with 50% or greater myometrial invasion have 6 to 7 fold increase in prevalence of pelvic and lumbo-aortic lymph node metastases compared to patients with myometrial invasion in whom it is absent or less than 50%.[4]

T2-weighted magnetic resonance imaging has been widely used for detection of myometrial invasion, but its accuracy is less satisfactory. To improve the usefulness of MR imaging for diagnostic purposes, other techniques are now being used; namely dynamic contrast enhanced MR imaging and diffusion weighted imaging.[11,12]

In this study, the authors determined the diagnostic accuracy of DWI in the pre-operative assessment of myometrial invasion by endometrial carcinoma. Results support that DWMRI can be used to discriminate between superficial and deep myometrial invasion.

In this study, the range of age was varying. A total of 85 patients were studied aged between 32 and 87 years with mean age of 59.2 years. This was in keeping with the western literature which also provided similar range of ages for the occurrence of endometrial cancer.[4,13]

No previous literature regarding association of myometrial invasion on MRI with regard to age or duration of symptoms was available. The results showed that MRI was highly significant in assessing myometrial invasion in patients of > 50 years and who presented with symptoms of < 6 months with p < 0.001.

In this study, MRI imaging was performed using 1.5 Tesla machine applying body and spine coil; the sensitivity, specificity, NPV and PPV of diffusion weighted images for diagnosis of myometrial invasion were 90%, 73%, 92% and 67%. These results are comparable with previous studies performed on 1.5 Tesla machine.[4,14]

Study conducted by Rechichi et al. enrolled a total of 62 patients who had proven endometrial carcinoma and who underwent pre-operative MR imaging examination on 1.5 Tesla machine and subsequent total hysterectomy.[4] They studied diagnostic performance of T2 weighted images alone, DWI alone and dynamic images alone, for superficial or deep myometrial invasion. In the assessment of tumor invasion, sensitivity, specificity, positive and negative predictive values of T2-weighted images were 92.3%, 76.5%, 60.0% and 96.3%, respectively. The corresponding values for dynamic images were 69.2%, 61.8%, 40.9% and 84.0%; and for DW images 84.6%, 70.6%, 52.4% and 92.3%. These are comparable to this study. They concluded that T2-weighted and DW imaging proved to be the most accurate techniques for tumor spread determination.

Another study conducted by Inada et al. on 1.5 Tesla machine discussed the feasibility and value of diffusion-weighted imaging in the detection of uterine endometrial cancer in comparison to conventional non-enhanced MR images.[13,14] They enrolled 23 patients taking histopathology as gold standard. In 19 out of 23 patients, endometrial cancers were detected only on T2-weighted images. In the remaining 4 patients, of whom 2 had co-existing leiomyoma, no cancer was detected on T2-weighted images. This corresponds to 83% detection sensitivity for the carcinomas. When DW images and fused DW images/T2-weighted images were used in addition to the T2-weighted images, cancers were identified in 3 of the remaining 4 patients in addition to the 19 patients (overall detection sensitivity of 96%). Hence, they also concluded that DW imaging can be helpful in the detection of uterine endometrial cancer in non-enhanced MR imaging. These findings have been further corroborated by Koplay et al. and Gallego et al. who also used additional ADC values for stronger results.[15,16]

A study conducted by Lin et al. used 3 Tesla machine to study the diagnostic accuracy of fused T2-weighted and high-b-value diffusion-weighted and magnetic resonance images for evaluation of myometrial invasion in patients with endometrial cancer.[13] They enrolled 48 consecutive patients aged 25 - 80 years (mean age = 57 years) who had endometrial cancer. Two radiologists interpreted the depth of myometrial invasion on T2-weighted images, dynamic contrast enhanced MRI, and fused T2-weighted and DW MRI. They concluded that for assessing any myometrial involvement, addition of fused T2-weighted and DWI to dynamic contrast-enhanced or T2-weighted imaging was significantly better compared with dynamic contrast-enhanced imaging alone (p < 0.001) or dynamic contrast-enhanced and T2-weighted (p = 0.001) imaging; T2-weighted imaging combined with fused T2-weighted and DW imaging was also better than dynamic contrast-enhanced and T2-weighted imaging (p = 0.001). These results are not comparable due to different techniques used in the two studies; however, according to this study

also, DWI plays a great role in assessment of myometrial invasion in endometrial carcinoma. Compared to these studies no intravenous contrast was needed in DWI imaging that were studied, hence saving the patient from adverse reactions of contrast and additional cost.

Several pitfalls were found in assessing the depth of myometrial invasion: non-visualization of a mass after curettage, a bulky polypoid tumor, a small uterus, a well-enhancing junctional zone, adenomyosis, leiomyoma, and retroversion of uterus. Some of these findings are consistent with those previously reported in literature.[13,1,17,18]

False-positive diagnoses, in detecting the presence of myometrial invasion, result in more radical surgery, involving more risk for the patient who might not actually require lymphadenectomy.[19] In this study, 14 false-positive diagnoses were made on the basis of DW MRI findings. In 3 patients, a bulky polypoid tumor distended the endometrial cavity, thus attenuating the myometrium. Two patients had a small uterus (< 5 cm in longitudinal diameter) and demonstrated marked thinning of the myometrium by a large polypoidal endometrial mass. Few of these errors were probably due to the thinned myometrium in elderly patients.

False-negative diagnoses, in detecting myometrial invasion, can lead to conservative surgical treatment (trans-vaginal or trans-abdominal hysterectomy without lymphadenectomy) in patients who are actually at risk for lymph node metastases.[20] In this study, 3 false-negative diagnoses were made, based on DW MRI findings. In 2 cases, the false-negative diagnoses involved lesions with myometrial invasion of 1 - 3 mm. These minimal amounts have little influence on the prognosis and prevalence of lymph node metastases. In the remaining case, however, the degree of myometrial invasion was relevant. This means that the staging errors may not be due to only insufficient spatial resolution of the techniques, but also due to subjective interpretative mistakes.

This study had few limitations. Only qualitative analysis of ADC was employed which can generate subjective error. No definite comparison was made with normal peripheral zone as a baseline to have better results. Single radiologist interpreted the results and inter-observer variability was not assessed. Established endometrial cancer in this study population, having biopsy and histopathological grading prior to MRI staging, was a major bias.

CONCLUSION

Results of the study suggest a potential role of DWI in evaluating depth of myometrial infiltration in patients with endometrial cancer. DWI MRI can play an important role in accurate staging and proper surgical and therapeutic planning of endometrial cancer. Overall sensitivity, specificity, PPV, NPV, and diagnostic accuracy of diffusion weighted images for diagnosis of myometrial invasion were 90%, 73%, 67%, 92% and 80%, respectively which is comparable to the international data available.

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